

REMARKS/ARGUMENTS

In response to the Office Action of April 20, 2006, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on August 25, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from consideration on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to recite that the biopolymer marker

consisting of SEQ ID NO:1 is indicative of a link to Type II diabetes. The instant specification discloses that this biopolymer marker was found to be related to Type II diabetes (Figure 1 and page 46, lines 4-12).

Claim 39 has been amended to clarify that the claimed method involves comparing the characteristic mass spectral profile of the biopolymer marker consisting of SEQ ID NO:1 to profiles obtained from a mass spectrometric analysis of an unknown sample in order to determine if the claimed biopolymer marker is present in the sample and thus indicative of a link to Type II diabetes. This determination is made by matching the reference mass spectral profile to a mass spectral profile obtained from the unknown sample. Claim 39 has also been amended to recite the steps (chromatography, electrophoresis, enzymatic digestion) used to prepare a sample for analysis by mass spectrometry. These preparatory steps increase the range, i.e. maximize elucidation, of peptides present in different concentrations that can be identified from a sample. See the abstract; page 24, line 14 to page 25, line 18; page 35, lines 19-22 and page 40, line 8 to page 46, line 3 of the instant specification as originally filed.

Claim 44 has been amended to correspond with the method of claim 39 as amended herein; i.e. claim 44 as amended herein is drawn to kit which is useful for carrying out the method of claim 39.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:1 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

* Please note that the Examiner's comments applied in the Office Action are single spaced herein to clearly delineate the Examiner's comments from Applicants' comments.

Rejection under 35 USC 101

Claim 1, as presented on January 23 and April 14, 2006, remains rejected under 35 USC 101 because the claimed invention is

allegedly not supported by either a specific, credible or a well-established utility.

The Examiner asserts that Applicant has identified band 6 of SEQ ID NO:1 in Figure 1 of the drawings. Applicants have disclosed in the remarks/arguments (page 26, paragraphs 1-2) that the biopolymer marker is present in only the diabetes II patients and not in the normal patients. However, in Figure 1 of the drawings, the biopolymer marker appears to be expressed in both normal and diabetes II patients. Therefore, the differential expression of SEQ ID NO:1 is not evident and the data results are ambiguous. The Examiner maintains that the correlation with respect to diabetes II is not exemplified or disclosed in the specification in a way that one of ordinary skill in the art could distinguish the differential expression in a diabetes II patient versus a normal patient. Therefore, one of ordinary skill in the art would not be able to distinguish a credible and specific or well established utility that SEQ ID NO:1 is linked to diabetes II. Although the MPEP does not require examples, however, the teaching provided must be substantial enough to enable one of ordinary skill in the art to ascertain the credibility of the evidence presented.

Accordingly, the Examiner concludes that the specification does not identify a substantial, credible or well-established utility for the sequence consisting of SEQ ID NO:1.

Applicants respectfully disagree with the Examiner's determination and assert that the claimed peptide (SEQ ID NO:1) has a specific, credible and well-established utility as a marker for Type II diabetes based upon the differential expression of the peptide in Type II diabetes versus a normal physiological state.

Rejections under 35 USC 101 have rarely been sustained by the courts because an applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement; i.e the Office should presume that a statement of utility made by an applicant is true (see MPEP 2107.02 III A and *In re Langer* 183 USPQ 297).

Thus, the Examiner should presume that the differential expression of the claimed biopolymer marker (SEQ ID NO:1) as exemplified in Figure 1 links the marker to Type II diabetes.

It is well known that pathological changes in an organism are reflected by changes observed in the serum protein pattern. In other words, proteins that undergo a change in expression (from the normal) are often indicative of disease. A diagnosis may be predicted based upon the similarity of an unknown sample pattern to a known pattern of disease. Mass spectrometry is a tool used to establish serum protein patterns.

Generally proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are often first subjected to separation by polyacrylamide gel electrophoresis. The separated protein bands which are deemed to be different between two comparable states are excised from the gel and subjected to further fragmentation by enzymes. These resulting peptides are then collected and purified by chromatography prior to identification by mass spectrometry. The peptides undergo step-wise degradation into sequence-defining fragments, i.e. the peptides are part of the original protein found in the serum sample. The mass spectral profiles generated are composed of parts of the original protein. See page 37, line 23 to page 40, line 6 of the instant specification.

In order for a rejection under 35 USC 101 to be appropriate

the Examiner must demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention (see *In re Joyce A. Cortright* 49 USPQ 2d 1464 1999).

It is respectfully submitted that the "link to Type II diabetes" asserted by Applicants was elucidated under real-world conditions according to the methodology set forth in the following steps:

I) isolating peptides from body fluid samples obtained from two groups of patients,

i) one group known to suffer from Type II diabetes; and

ii) one group of normal, healthy control patients;

II) carrying out the protocols disclosed in the specification (see pages 37-47);

III) comparing the expression bands from the two groups of patients as evidenced in gels (such as that shown in Figure 1);

IV) subjecting the observed expression pattern to the criteria as disclosed at page 11, lines 9-20 of the instant specification;

V) excising bands that are differentially expressed between the groups, and, submitting the peptides present within the excised bands for sequence identification by mass spectrometry.

The instant inventors, using the above-described methodology in a real-world environment, thereby elucidated and identified SEQ ID NO:1 as a fragment of an apolipoprotein protein showing

differential expression between a normal state and a diseased state. Thus, the instantly claimed link to Type II diabetes was established as evidenced by the observed differential expression. Applicants respectfully submit that the "link to Type II diabetes", evidenced by the differential expression shown in Figure 1, supports the usefulness of the claimed peptide (SEQ ID NO:1) for diagnosis and/or treatment of Type II diabetes.

The claimed biopolymer marker (SEQ ID NO:1) was identified as a fragment of an apolipoprotein protein, having a molecular weight of 1215 daltons, by mass spectrometric analysis. Mass spectral profiles are reproducible, and are typically published for reference purposes.

Thus, any skilled artisan, in a real-world context, and without significant further research, could utilize the mass spectral profile of the claimed peptide as a reference for comparing with mass spectral profiles of peptides obtained from unknown samples to test the unknown samples for a link to Type II diabetes, thereby establishing a disclosed specific and substantial credible utility.

Accordingly, Applicants respectfully submit that the Examiner has failed to demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.

The Examiner asserts that in Figure 1 of the drawings, the biopolymer marker appears to be expressed in both normal and diabetes II patients. Therefore, the differential expression of SEQ ID NO:1 is not evident and the data results are ambiguous. The Examiner maintains that the correlation with respect to diabetes II is not exemplified or disclosed in the specification in a way that one of ordinary skill in the art could distinguish the differential expression in a diabetes II patient versus a normal patient.

Thus, Applicants contend that the Examiner appears to doubt the credibility of Applicants' asserted utility for the claimed peptide as a marker for Type II diabetes.

If an Examiner doubts the credibility of an asserted utility, the Examiner must show that the asserted utility is wholly inconsistent with contemporary knowledge in the art (see *In re Gazave* 379 F.2d 973, 978 CCPA 1967).

The claimed peptide (SEQ ID NO:1) was resolved from Band 6 of the gel shown in Figure 1. The peptides present in Band 6 have migrated to the same position in samples obtained from patients having Type II diabetes (lanes 2-6, as read from the left). In contrast, no bands are evident in the corresponding position of Band 6 in the samples obtained from normal control patients. Thus, the peptides of Band 6 are not found in the samples obtained from normal, healthy control patients (see Figure 1 as originally filed and as filed on April 14, 2006). Accordingly, the claimed peptide (SEQ ID NO:1) is differentially expressed in Type II diabetes compared to a normal physiological state.

As established in the previous Response filed on January 23, 2006, it is well-known that in the search for specific biomarkers proteins found to be differentially expressed between "disease" and "normal" are frequently identified as targets for diagnostics and/or therapeutics. See pages 26-28 of the previous Response and the attached Patterson reference. Therefore, Applicants' identification of SEQ ID NO:1 as a marker for Type II diabetes based upon differential expression is consistent with common practice in proteomics.

Accordingly, Applicants respectfully submit that the Examiner has failed to show that Applicants' asserted utility for the claimed marker (SEQ ID NO:1) is wholly inconsistent with contemporary knowledge in the art.

Furthermore, an Examiner must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe applicant's assertion of utility (see *In re Brana* 34 USPQ 2d 1436).

Although the prior art does not specifically recognize that the claimed biopolymer marker consisting of SEQ ID NO:1, a fragment of an apolipoprotein, is related to Type II diabetes, it does recognize an association between abnormalities in apolipoprotein metabolism and Type II diabetes (for example, see attached abstract of Duvillard et al. *European Journal of Clinical Investigation* 30(8):685-694 2000; reference 1). Furthermore, it is also known

that an increased number of circulating apolipoproteins is found in the bodily fluids of patients having Type II diabetes (Duvillard; reference 1). Thus, it is very likely that the levels and/or function of the apolipoprotein that the claimed peptide was derived from is altered in Type II diabetes.

Applicants respectfully submit that an artisan of ordinary skill would find the suggestion of a link between the claimed peptide (SEQ ID NO:1) and Type II diabetes to be reasonable. As was discussed extensively herein and in the prior Response filed on January 23, 2006, when one of skill in the art observes the differential expression of the claimed biopolymer marker (SEQ ID NO:1) between Type II diabetes patients and normal patients; one of skill in the art will connect this marker with diagnostics and/or therapeutics for Type II diabetes.

At page 46 of the specification as originally filed , SEQ ID NO:1 is identified as a fragment of an apolipoprotein. As mentioned above, abnormalities in apolipoprotein metabolism are known to be associated with Type II diabetes (see reference 1). Additionally, insulin resistance, an altered plasma lipid profile and Type II diabetes are known to be linked (see attached abstract of Serrano Rios European Journal of Clinical Investigation 28:14 1998; reference 2). One of ordinary skill in the art, considering the known abnormalities of plasma apolipoproteins suffered by the Type II diabetic patient, upon observation of the differential

expression of SEQ ID NO:1 in Type II diabetes versus normal control, would find it reasonable to believe that this peptide is linked to Type II diabetes.

Accordingly, Applicants respectfully submit that one of ordinary skill in the art would not doubt the veracity of Applicants asserted utility for the claimed peptide (SEQ ID NO:1).

Furthermore, situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a disease state versus expression in a normal physiological state.

For example, Andreassen et al. disclose a study wherein the differences in concentration of β -amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreassen et al. found that levels of CSF- β -amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF- β -amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreassen et al. Archives of Neurology 56(6):673-680 1999; reference 3).

Since the data of Andreassen et al. was available in the art at

the time of the invention, one of skill in the art would be familiar with such practice (suggestion of a differentially expressed peptide for diagnostics) and thus likely to find that linking the observed differential expression of the claimed biopolymer marker (SEQ ID NO:1) to the suggested use of diagnostics and/or therapeutics of Type II diabetes is plausible.

It has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (see MPEP 2164.07 I C).

Figure 1 establishes that the claimed biopolymer marker (SEQ ID NO:1) is differentially expressed between Type II diabetes patients and normal patients. As pointed out above, one of skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. Thus, differential expression of a peptide between a disease state and a normal state is enough information to label a peptide a "marker" for the disease condition, no additional validation, comparison with other diseases, or further research is necessary.

Accordingly, Applicants respectfully contend that one of skill in the art would believe, based upon the information in the specification in light of the knowledge in the prior art, that the

claimed biopolymer marker (SEQ ID NO:1) is more likely than not to be a marker of Type II diabetes.

The Examiner is reminded that the purpose of the patent system is to promote the progress of science and the useful arts (see "Introduction" of the MPEP and Article 1, section 8 of the US Constitution). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote the progress of science and may discourage further medical research. The progress of science usually occurs in a "piecemeal" fashion; meaning that a "discovery" does not arise by itself but often proceeds through multiple "discoveries". For example, a new drug to treat Type II diabetes is a "discovery" while peptide markers, such as the instant invention are smaller "discoveries" which lead to the "discovery". These smaller "discoveries" , such as the instant invention, should be allowed patent protection because they promote the progress of science by leading to further, larger "discoveries".

The decision in *In re Brana* (34 USPQ2d 1436 and MPEP 2107.01 III) lends support to this argument as well since the Federal Circuit stated that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in

order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Additionally, in contrast to the holding in *Fisher* (see *In re Fisher* 76 USPQ 2d 1225 2005), where expressed sequence tags (ESTs) were deemed not to have a substantial and credible utility because the disclosed uses were not specific to the claimed ESTs but instead were generally applicable to any EST, the instantly claimed peptide does indeed evidence a specific use as a marker linked to Type II diabetes supported by data specifically directed to patients having Type II diabetes.

As noted above, one could, without any further research, utilize the mass spectral profile of the claimed peptide as a reference for comparing with mass spectral profiles of peptides obtained from unknown samples to test the unknown samples for a link to Type II diabetes. Thus, the instant invention satisfies the *Fisher* test for disclosure of a substantial utility by showing that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research, and thus, a significant and presently available "real-world" benefit to the public is disclosed.

In conclusion, based upon all of the above arguments,

Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has a specific, substantial and well-established credible utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on January 23 and April 14, 2006, remains rejected under 35 USC 112, first paragraph.

Specifically, the Examiner asserts that since the claimed invention is not supported by either a specific, substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response that the claimed invention has both a clear asserted utility and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (SEQ ID NO:1) as a marker for Type II diabetes; therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

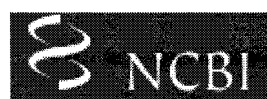
Respectfully submitted,

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☐ 1: Eur J Clin Invest. 2000 Aug;30(8):685-94.



Links

Metabolic abnormalities of apolipoprotein B-containing lipoproteins in non-insulin-dependent diabetes: a stable isotope kinetic study.

Duvillard L, Pont F, Florentin E, Galland-Jos C, Gambert P, Verges B.

INSERM U 498-Metabolisme des Lipoproteines Humaines et Interactions Vasculaires, Faculte de Medecine, Dijon, France.

BACKGROUND: Kinetic abnormalities of apolipoprotein B (apoB)-containing lipoproteins in noninsulin-dependent diabetes mellitus (NIDDM) remain poorly understood. To get further insight into these abnormalities we performed a stable isotope kinetic experiment comparing the metabolism of apoB-containing lipoproteins in moderately severe NIDDM patients and healthy control subjects. **METHODS:** The study was performed in the fed state. Subjects underwent a primed infusion of 0.7 mg kg⁻¹ of L-[1-(13)C]leucine followed by a 16-h constant infusion of 0.7 mg kg⁻¹ h⁻¹. [13C]Leucine enrichment in apoB was measured by gas chromatography/combustion/isotope ratio mass spectrometry. **RESULTS:** In NIDDM patients, we observed a 3.49- and 4.52-fold increase of very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) apoB plasma concentrations, respectively (P<0.01). VLDL apoB production was increased by 41% (P<0.05) and fractional catabolic rate towards IDL and low-density lipoprotein (LDL) was decreased by 61% (P<0.05). The increased IDL apoB plasma concentration was also related to a major catabolic defect (-78%; P<0.01). For most patients, plasma LDL apoB concentration was comparable to that of controls. Nevertheless, LDL apoB metabolism was impaired in NIDDM subjects, with both a decreased LDL catabolic rate (-28%; P<0.05) and a trend towards a diminished synthesis. **CONCLUSION:** NIDDM is associated with multiple apoB metabolism abnormalities that are potentially atherogenic. In addition to the increased number of circulating VLDL and IDL particles, the increased residence time observed on all apoB-containing lipoproteins may promote the development of atherosclerotic lesions, by potentiating their oxidizability.

PMID: 10964160 [PubMed - indexed for MEDLINE]

Related Links

Significant improvement of apolipoprotein B-containing lipoprotein metabolism by insulin treatment in patients with non-insulin-dependent diabetes mellitus. [Diabetes Care. 2000]

Early kinetic abnormalities of apoB-containing lipoproteins in insulin-resistant women with abdominal obesity. [Arterioscler Thromb Vasc Biol. 2002]





Effect of insulin therapy on metabolic fate of apolipoprotein B-containing lipoproteins in NIDDM. [Diabetes. 1990]

VLDL and IDL apolipoprotein B-100 kinetics in familial hypercholesterolemia due to impaired LDL receptor function or to defective apolipoprotein B-100. [J Lipid Res. 1998]

Interrelationships between human apolipoprotein A-I and apolipoproteins B-48 and B-100 kinetics using stable isotopes. [Arterioscler Thromb Vasc Biol. 2004]

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European Journal of
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Relationship between obesity and the increased risk of major complications in non-insulin-dependent diabetes mellitus

Serrano Rios

Obesity and non-insulin-dependent diabetes mellitus (NIDDM) are closely linked. They frequently occur together in patients, and body mass index (BMI) is the strongest risk factor for the development of NIDDM. Both obesity and NIDDM are also major causes of morbidity and mortality from atherogenic macrovascular disease, and they are independent risk factors for coronary heart disease. The risk of developing NIDDM and cardiovascular disease is affected by the regional distribution of body fat. Visceral obesity is associated with a higher degree of risk than peripheral obesity. The metabolic and circulatory changes associated with visceral obesity lead to the development of insulin resistance and increased lipoprotein synthesis. For example, the change in the population profile of lipoproteins in the blood, and alterations in the levels of oxidative stress lead to an increased cardiovascular and macrovascular risk. The changes in lipid metabolism also affect haemorrhheological function. They have been linked to decreased fibrinolysis (a serious cardiovascular risk factor) through elevated levels of plasminogen activator inhibitor factor, high blood viscosity, and increased erythrocyte aggregability. Increased BMI also appears to be associated with endothelial dysfunction, which is a major factor in atheroma plaque formation and development of thrombosis. Visceral obesity therefore adds a significant burden to the already increased cardiovascular risk inherent in NIDDM. However, even moderate weight loss may successfully reverse the majority of changes seen with visceral obesity.

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- M. ÖGREN, H. ERIKSSON, D. BERGQVIST & N.-H. STERNBY. (2005) Subcutaneous fat accumulation and BMI associated with risk for pulmonary embolism in patients with proximal deep vein thrombosis: a population study based on 23 796 consecutive autopsies. *Journal of Internal Medicine* 258:2, 166-171

Abstract

References

Full Text Article

PDF

- B. STRATMANN and D. TSCHOEPE. (2005) Hemostatic abnormalities associated with obesity and the metabolic syndrome. *Journal of Thrombosis and Haemostasis* 3:5, 1078-1080

Summary

References

Full Text Article

PDF

- T. Haak, A. Tiengo, E. Draeger, M. Suntum and W. Waldhäusl
(2005) Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 7:1, 56-64

Abstract

References

Full Text Article

PDF

- Ebru Tarim, Tayfun Bagis, Esra Kilicdag, Serkan Erkanli, Erdogan Aslan, Nurzen Sezgin and Esra Kuscu
(2004) Elevated plasma homocysteine levels in gestational diabetes mellitus. *Acta Obstetrica et Gynecologica Scandinavica* 83:6, 543-547

Abstract

References

Full Text Article

PDF

- Wayne S. Cutfield, Craig A. Jefferies, Wendy E. Jackson, Elizabeth M. Robinson and Paul L. Hofman
(2003) Evaluation of HOMA and QUICKI as measures of insulin sensitivity in prepubertal children. *Pediatric Diabetes* 4:3, 119-125

Abstract

References

Full Text Article

PDF

- T. A. Jones, M. Sautter, L. F. Van Gaal and N. P. Jones
(2003) Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. *Diabetes, Obesity and Metabolism* 5:3, 163-170

Abstract

References

Full Text Article

PDF

- A. Gokcel, M. Baltali, E. Tarim, T. Bagis, Y. Gumurdulu, H. Karakoş, F. Yalcin, M. Akbaba and N. Guvener
(2003) Detection of insulin resistance in Turkish adults: a hospital-based study. *Diabetes, Obesity and Metabolism* 5:2, 126-130

Abstract

References

Full Text Article

PDF

- E. Standl
(1999) Cardiovascular risk in type 2 diabetes. *Diabetes, Obesity and Metabolism* 1:s2, 24-36

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Relationship between obesity
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Arch Neurol. 1999 Jun;56(6):655-6.

Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease.

Andreasen N, Hesse C, Davidsson P, Minthon L, Wallin A, Winblad B, Vanderstichele H, Vanmechelen E, Blennow K.

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OBJECTIVES: To study the diagnostic potential of the 42 amino acid form of beta-amyloid (beta-amyloid(1-42)) in cerebrospinal fluid (CSF) as a biochemical marker for Alzheimer disease (AD), the intra-individual biological variation of CSF-beta-amyloid(1-42) level in patients with AD, and the possible effects of differential binding between beta-amyloid and apolipoprotein E isoforms on CSF-beta-amyloid(1-42) levels. **DESIGN:** A 20-month prospective follow-up study. **SETTING:** Community population-based sample of consecutive patients with AD referred to the Pitea River Valley Hospital, Pitea, Sweden. **PATIENTS:** Fifty-three patients with AD (mean +/- SD age, 71.4 +/- 7.4 years) diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria and 21 healthy, age-matched (mean +/- SD age, 68.8 +/- 8.0 years) control subjects. **MAIN OUTCOME MEASURES:** Cerebrospinal fluid beta-amyloid(1-42) level--analyzed using enzyme-linked immunosorbent assay--and severity of dementia--analyzed using the Mini-Mental State Examination. **RESULTS:** Mean +/- SD levels of CSF-beta-amyloid(1-42) were decreased ($P < .001$) in patients with AD (709 +/- 304 pg/mL) compared with controls (1678 +/- 436 pg/mL). Most patients with AD (49 [92%] of 53 patients) had reduced levels (< 1130 pg/mL). A highly significant correlation ($r = 0.90$; $P < .001$) between baseline and 1-year follow-up CSF-beta-amyloid(1-42) levels was found. There were no significant correlations between CSF-beta-amyloid(1-42) level and duration ($r = -0.16$) or severity ($r = -0.02$) of dementia. Low levels were also found

Related Links

High cerebrospinal fluid tau and low amyloid beta42 levels in the clinical diagnosis of Alzheimer disease and relation to apolipoprotein E genotype. [Arch Neurol. 1998]

Evaluation of CSF-tau and CSF-Abeta42 as diagnostic markers for Alzheimer disease in clinical practice. [Arch Neurol. 2001]

Decreased beta-amyloid1-42 and increased tau levels in cerebrospinal fluid of patients with Alzheimer disease. [JAMA. 2003]

Cerebrospinal fluid tau protein as a biochemical marker for Alzheimer's disease: a community based follow up study. [Arch Neurol Neurosurg Psychiatry. 1998]

Cerebrospinal fluid levels of total-tau, phospho-tau and A beta 42 predicts development of Alzheimer's disease in patients with mild cognitive impairment. [Alzheimer Dis Suppl. 2003]

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in patients with mild dementia (Mini-Mental State Examination score, >25). CONCLUSIONS: The sensitivity of CSF-beta-amyloid(1-42) level as a diagnostic marker for AD is high. The intra-individual biological variation in CSF-beta-amyloid(1-42) level is low. Low CSF-beta-amyloid(1-42) levels are also found in the earlier stages of dementia in patients with AD. These findings suggest that CSF-beta-amyloid(1-42) analyses may be of value in the clinical diagnosis of AD, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult.

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